Synthetic Lethality in Cancer Treatment: Current status of PARP Inhibitors

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Inhibitors of poly(ADP-ribose)polymerase (PARP) may be applied to cancer treatment in a number of different ways.

They may be used as single agents in the treatment of cancers arising in patients who are carriers of a BRCA1 or BRCA2 mutation. Since PARP is involved in the repair of single strand breaks in DNA, treatment with a PARP inhibitor leads to an accumulation of such breaks. Cancers arising on a background of a BRCA mutation lack the homologous recombination repair pathway and are uniquely unable to survive single strand breaks. This mechanism is known as "synthetic lethality" in which two molecular lesions combine to have a lethal effect on the cell, although neither of them is harmful individually. Clinical "proof of principle" for this mechanism has been demonstrated using olaparib in an expanded Phase I study and in two Phase II studies where response rates in the region of 40% were seen in breast and ovarian cancer[1,2,3].

In vitro, and in experimental animal models, PARP inhibitors have been shown specifically to potentiate monomethylating agents and topoisomerase I inhibitors regardless of their BRCA status. A Phase I and Phase II study of AG014699 in combination with temozolomide has shown promising response rates in patients with metastatic melanoma[4,5].

PARP inhibitors have also been shown to potentiate chemotherapy treatment in patients whose tumours are expected to have a BRCA-like phenotype – that is to have a reduced ability to undertake homologous recombination repair. BSI 201 has been the subject of a randomised Phase II study in combination with gemcitabine and carboplatin in triple negative breast cancer.

PARP inhibitors also have potential as radio-sensitising agents and are a new class of drugs with potential in this area, since previous trials have focussed on hypoxic cell sensitisation.

Finally there is the possibility that PARP inhibitors might be given prophylactically to known BRCA mutation carriers, who have a very high lifetime probability of developing various cancers.

There are currently at least nine PARP inhibitors in development, listed below. We can expect to see extensive applications of PARP inhibitors with the major ones probably focussing on patients with tumours that are deficient in homologous recombination repair.

Agent	Company	Route	Clinical Status
AG014699	Pfizer	IV (oral)	Phase I/II combos
Olaparib (AZD2281)	AstraZeneca	Oral	Phase II/III combos
ABT888	Abbott	Oral	Phase I/II combos
BSI-201	BiPar / Sanofi-Aventis	Iv	Phase II/III combos
INO-1001	Inotek	Iv	Phase 1b complete
GP121016	Eisai / MGI Pharma	Oral	Phase I
CEP-9722	Cephalon	Oral	Phase I
MK4827	Merke	Oral	Phase I
BMN-673	Biomarin / LEAD		Preclinical

References

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2. Tutt et al. J Clin Oncol 27:15s, 2009 (suppl; abstr 5500)

3. M. W. Audeh et al, 2009 ASCO Annual Meeting Proceedings 27 abstract 5500

4. Plummer R, et al. Phase I Study of the Poly (ADP-Ribose) Polymerase Inhibitor, AG014699, in Combination with Temozolomide in Patients with Advanced Solid Tumors. Clinical Cancer Research 14(23):7917-7923, 2008

5. Plummer R, Lorigan P, Evans J, et al. J Clin Oncol 2006;24:456S